Pluripotency factor-mediated expression of the leptin receptor (OB-R) links obesity to oncogenesis through tumor-initiating stem cells.

Journal: Proc Natl Acad Sci U S A

Publication Year: 2012

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PubMed link: 22207628

Funding Grants: CIRM Stem Cell Biology Training Program

Public Summary:
These findings raise the possibility that leptin signaling to OB-Rb functions as an independent signaling axis to maintain the pluripotent state in mouse blastocysts. Such a function may extend to human embryonic development.

Scientific Abstract:
Misregulation of a pluripotency-associated transcription factor network in adult tissues is associated with the expansion of rare, highly malignant tumor-initiating stem cells (TISCs) through poorly understood mechanisms. We demonstrate that robust and selective expression of the receptor for the adipocyte-derived peptide hormone leptin (OB-R) is a characteristic feature of TISCs and of a broad array of embryonic and induced pluripotent stem cells and is mediated directly by the core pluripotency-associated transcription factors OCT4 and SOX2. TISCs exhibit sensitized responses to leptin, including the phosphorylation and activation of the pluripotency-associated oncogene STAT3 and induction of Oct4 and Sox2, thereby establishing a self-reinforcing signaling module. Exposure of cultured mouse embryonic stem cells to leptin sustains pluripotency in the absence of leukemia inhibitory factor. By implanting TISCs into leptin-deficient ob/ob mice or into comparably overweight Lepr(db/db) mice that produce leptin, we provide evidence of a central role for the leptin-TISC-signaling axis in promoting obesity-induced tumor growth. Differential responses to extrinsic, adipocyte-derived cues may promote the expansion of tumor cell subpopulations and contribute to oncogenesis.

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